REMARKS/ARGUMENTS

Claims 18-66 are pending in the above-referenced patent application; claims 47-66 are currently under examination; claims 18-46 have been withdrawn from consideration as being drawn to a non-elected invention pursuant to a Restriction Requirement.

The Invention

The present invention is directed, in part, to a method of inhibiting the generation of active thrombin on the surface of a cell within an atherosclerotic plaque within a mammal, the method comprising producing an ER resident chaperone protein in the cell within an. In one embodiment, the ER resident chaperone protein is produced by introducing into the cell a polynucleotide encoding an ER resident chaperone protein. In another embodiment, the ER resident chaperone protein is produced by administering to the cell a compound, *e.g.*, a cytokine, that induces expression or activation of an endogenous ER resident chaperone protein.

Objection to the Drawings

The Office Action indicates that the drawings are considered informal and that formal drawings need to be filed upon receiving a Notice of Allowance.

Upon receiving a Notice of Allowance, Applicants will file formal drawings, making sure that they address the Examiner's concerns.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 47-54 have been rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps. In making this rejection, the Office Action alleges that the claims do not recited the steps which lead to the production of the ER resident chaperone protein in the cell (*see*, page 3 of the Office Action). The Office Action further alleges that without a clear indication of the methods steps which result in the production of an ER resident chaperone protein in the cell, the method is unclear and indefinite (*see*, page 3 of the Office Action). Applicants respectfully traverse this rejection.

The pending claims are based on the surprising discovery that the generation of active thrombin on the surface of a cell within an atherosclerotic plaque within a mammal can be inhibited by producing an ER resident chaperone protein in the cell. As such, the pending claims do, in fact, recite the essential step of the claimed method, *i.e.*, producing an ER resident chaperone protein in a cell within an atherosclerotic plaque within a mammal. As explained in the specification and as pointed out in the Office Action, there are a number of different methods that can be used to produce an ER resident chaperone protein in the cell. However, the particular method used to produce an ER resident chaperone protein is ***not*** an essential step of the claimed method. Again, what is essential to the claimed method is that an ER resident chaperone protein is produced in a cell within an atherosclerotic plaque within a mammal, and the claims clearly recite this step.

In view of the foregoing remarks, it is clear that the presently claimed methods do recite the "essential" steps. Accordingly, Applicants request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

First Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 47-54 and 60 are rejected under 35 U.S.C. § 112, second paragagraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In support of this rejection, the Office Action acknowledges that the instant claims encompass administering to the cell a compound which induces the expression or activation of an endogenous ER resident chaperone protein. The Office Action alleges, however, that there is insufficient description of the compounds encompassed by the claims and one of skill in the art would not be able to recognize any of the claimed compounds other than the two described [cytokines and mucleic acids] without performing additional experimentation to determine which compounds induced chaperone expression or activated the chaperone(s) (*see*, page 4 of the Office Action). Applicants ***disagree***.

Applicants respectfully point out that in addition to cytokines and nucleic acids, the specification provides a list of other compounds that can also be used to induce the expression or activation of an ER resident chaperone protein (*see, e.g.*, the specification at page 16, line 3 through page 17, line 12, and page 23, line 26 through page 24, line 3). As the Examiner is aware, the specification teaches that the presently claimed method can use any known ER resident chaperone protein (*see*, page 16, lines 3-15 of the specification). The specification provides both the nucleic acid and amino acid sequences of the ER resident chaperone protein GRP78/BiP, which were in the public domain (GenBank Accession number AJ271729) (*see*, pages 46 and 47 of the specification). The specification additionally provides references to the sequences of other ER resident chaperone proteins that can be used in the present invention, such as GRP94 (GenBank Accession No. M26596), calnexin (GenBank Accession No. M94859), calreticulin (GenBank Accession No. NM_004343), and reticulocalbin (*see*, page 16, lines 6-13 of the specification). The specification also discloses that a sequence of human calnexin (IP90) (GenBank Accession number L10284) was also in the public domain prior to the filing of the present application.

Moreover, the specification teaches that any treatment, compound, protein, or polynucleotide can be used that decreases the level of free calcium in the secretory pathway. Examples of such compounds include GRP78/BiP, reticulocalbin, Calreticulin, or Calnexin (*see*, the specification at page 16, lines 16-23). In addition, the specification teaches that any treatment, factor or condition that increases the level or activity of an ER resident chaperone protein can be used, including those that adversely affect protein processing and folding in the ER (*e.g.*, homocysteine and other sulfhydryl-reducing agents, unassembled protein subunits within the ER, overexpression and aggregation of proteins within the ER), treatments known to affect cellular glycosylation (*e.g.*, glucose starvation, tunicamycin, 2-deoxyglucose, glucosamine), treatments known to affect intracellular Ca^{2+} levels (*e.g.*, calcium ionophores A23187 and ionomycin, calcium chelating agents, EGTA, calcium ATPase inhibitors, thapsigargin), or other treatments and/or conditions including ethanol, hypoxia, insulin, tissue injury, and low extracellular pH.

In addition to the compounds provided in the specification, other compounds known in the art to induce the expression or activation of an ER resident chaperone protein can also be used in the presently claimed method. Examples of such compounds include those disclosed in the Nakai *et al.* and Cheng *et al.* references, both of which were cited by the Examiner in the previous Office Action.

As such, contrary to the allegations in the Office Action, the specification does, in fact, provide a list of numerous compounds that can be used to induce the expression or activation of an ER resident chaperone protein. Moreover, as explained below, the specification provides screening methods that can be used, ***without undue experimentation***, to screen a given compound for its ability to induce the expression or activation of an ER resident chaperone protein. Accordingly, at the time the present application was filed, Applicants had full possession of the presently claimed invention. Accordingly, Applicants request that the § 112, first paragraph, rejection be withdrawn.

Second Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 47-66 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. The Office Action states that while being enabled for a method for inhibiting the generation of active thrombin on the surface of a cell within a mammal wherein said method comprises (1) directly administering to said cell a polynucleotide which encodes and expresses GRP78/BiP, or (2) administering to said cell interleukin-3, the specification does not reasonably provide enablement for the full scope encompassed by the claims.

In support of the above rejection, the Office Action raises the following two enablement concerns: (1) the broadest claim encompasses administering any compound that induces the expression or activation of an endogenous ER resident chaperone protein; and (2) the broadest claim encompasses administering a nucleic acid that encodes and expresses any ER resident chaperone protein to the target cell by any means of administration such as systemic administration. Each of these concerns will be addressed, in turn, below.

a. Overview of the Law of Enablement

A particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without ***undue*** experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. It is important to note that the possibility that some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, MPEP § 2164.01.
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP § 2164.06, citing *In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988).
>
> As MPEP § 2164.02 states, "[a] rigorous or an invariable exact correlation is not required" between a particular model and a specific condition.
>
> As set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments."

b. The Specification Provides Both Screening Methods and Lists of Compounds that Can be Used to Induce the Expression or Activation of ER Resident Chaperone Proteins

The first concern raised in the Office Action is that the broadest claim encompasses administering any compound that induces the expression or activation of an ER resident chaperone protein. The Office Action acknowledges that the specification teaches that cytokines, such as IL-3, can be used to induce the expression or activation of an ER resident

chaperone protein, but alleges that no other compounds are disclosed (*see*, pages 4 and 5 of the Office Action).

As explained above, in addition to nucleic acids and cytokines, the specification provides a list of other compounds that can also be used to induce the expression or activation of an ER resident chaperone protein (*see*, *e.g.*, the specification at page 16, line 3 through page 17, line 12, and page 23, line 26 through page 24, line 3). Moreover, in addition to the compounds provided in the specification, other compounds known in the art to induce the expression or activation of an ER resident chaperone protein can also be used in the presently claimed method. Examples of such compounds include those disclosed in the Nakai *et al.* and Cheng *et al.* references, both of which were cited by the Examiner in the previous Office Action.

In addition to providing a list of diverse compounds that can be used to induce the expression or activation of an ER resident chaperone protein, the specification, as originally filed, discloses and claims screening methods for determining whether a given compound induces the expression or activation of an ER resident chaperone protein (*see*, *e.g.*, the specification at page 24, line 4 through page 34, line 29 and originally filed claims 38-45). Using such screening methods, one of skill in the art can ***readily*** screen any compound for its ability to induce the expression or activation of an ER resident chaperone protein ***without*** undue experimentation.

Again, as set forth in MPEP § 2164.96:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Clearly, in the present case, any experimentation carried out in connection with the presently claimed method would be entirely ***routine*** in view of the significant amount of guidance provided in the specification regarding the compounds that can be used to induce expression or activation of an ER resident chaperone protein and the methods that can be used for screening the compounds of interest for the desired activity.

c. *The Specification Provides Both Viral and Non-Viral Modes for Delivering Nucleic Acids to Cells*

The second issue raised by the Examiner is that the broadest claim encompasses administering a nucleic acid that encodes and expresses any ER resident chaperone protein to the target cell by any means of administration such as systemic administration.

As explained above, the specification teaches that the presently claimed method can use any known ER resident chaperone protein (*see*, page 16, lines 3-15 of the specification). The specification provides both the nucleic acid and amino acid sequences of the ER resident chaperone protein GRP78/BiP, which were in the public domain (GenBank Accession number AJ271729) (*see*, pages 46 and 47 of the specification). The specification additionally provides references to the sequences of other ER resident chaperone proteins that can be used in the present invention, such as GRP94 (GenBank Accession No. M26596), calnexin (GenBank Accession No. M94859), calreticulin (GenBank Accession No. NM_004343), and reticulocalbin (*see*, page 16, lines 6-13 of the specification). The specification also discloses that a sequence of human calnexin (IP90) (GenBank Accession number L10284) was also in the public domain prior to the filing of the present application.

Moreover, the specification provides teachings regarding both viral and non-viral modes for delivering nucleic acids to cells *in vivo*. In support of this position, it is once again pointed out that the specification cites over 39 references that provide more than ample evidence of success using viral and non-viral modes of delivery, and their disclosures provide protocols that enable predictable application of viral and non-viral delivery systems for different nucleic acid sequences of interest. Moreover, at the time of the present invention, liposomal formulations for delivering nucleic acids systemically were known to those of skill in the art (*see, e.g.*, PCT Publication No. 99/39741). Using these lipid formulations as well as others known lipoplex or DNA-cationic liposome formulations, one of skill in the art, at the time of the present inveniton, could deliver nucleic acids by systemic administration. As such, the teachings of the specification, coupled with the general knowledge in the art at the time of the present invention, provide modes of delivery that allow for direct as well as systemic administration of

nucleic acids. As such, undue experimentation would ***not*** be needed to carry out the methods of the present invention.

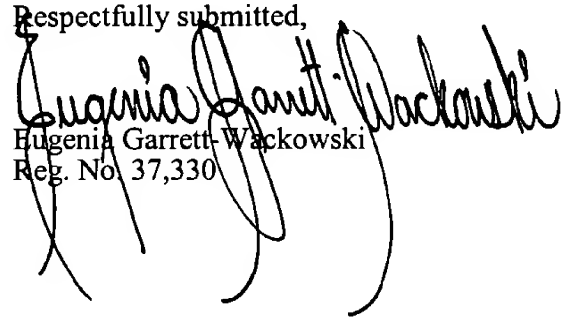
In view of the foregoing, it is readily apparent that the specification enables the full scope of the claims and, thus, undue experimentation is not required to practice the full scope of the claims. Accordingly, Applicants request that the § 112, first paragraph, rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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